

REMARKS/ARGUMENTS

Claims 61 – 81 and 93 – 104 are pending and stand rejected in the instant application. Applicants have amended claims 61, 68, 69, 72, 80 and 81. Support for these amendments can be found throughout the specification, no new matter is introduced.

Specification

The specification was objected to because it contains an embedded hyperlink and/or other form of browser-executable code. The specification has been amended to delete the embedded hyperlink and/or other form of browser executable code.

Information Disclosure Statement

While most references on the previously filed Information Disclosure Statements has been considered, three of them were either not considered, or considered partially, due to incomplete copies from Applicant's errors. Those three references are submitted herein again in a new IDS. Acknowledgement and consideration of these documents are greatly appreciated.

Claim rejections – 35 USC §101

Claims 61 – 81 and 93 - 104 are rejected under 35 USC § 101 for, in the Examiner's view, lacking utility. More specifically, the Examiner asserts that the claimed

invention is not supported by a specific or substantial utility. Applicants respectfully traverse this rejection for the reasons set forth below.

Applicants first note that the utility requirement of § 101 is met either if the claimed subject matter has a “well-established” utility, or if a substantial, specific, and credible utility is disclosed in the specification.

An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (2) the utility is specific, substantial, and credible.

Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098 (Jan. 5, 2001). For example, “some uses can be immediately inferred from a recital of certain properties.” *In re Folkers*, 344 F.2d 970, 974 (C.C.P.A. 1965) (explicitly undisturbed by *Brenner v. Manson*, 383 U.S. 519, 535 n.23 (1966) and *In re Kirk*, 376 F.2d 936, 949 (C.C.P.A. 1967) (Rich, J., dissenting)).

The instant application relates to a single exon nucleic acid microarray, comprising a plurality of nucleic acid probes addressably disposed upon a substrate, wherein each of said probes include genomic sequence of at least one predicted exon of a eukaryotic genome, at least 50% of said probes include genomic sequence of no more than one exon of said eukaryotic genome, said eukaryotic genome averaging at least one

intron per gene, and wherein said plurality of nucleic acid probes averages at least 50 nt in length.

In the utility rejection section of the office action, the Examiner acknowledges that the “the claimed arrays could be useful”. However, the Examiner states that the utilities “are not specific for the claimed nucleic acid array because”, in the Examiner’s view, “they are utilities that could be ascribed to any nucleic acid array with fragments of genomic DNA from open reading frames of a eukaryotic genome”. Applicants respectfully disagree.

As summarized above, the single exon nucleic acid microarrays of the instant application contains probes derived from genomic sequence of at least one predicted exon of a eukaryotic genome. The probes on the claimed microarrays are NOT from any random “fragments of genomic DNA from open reading frames of a eukaryotic genome” as the Examiner suggested. The probes are identified by various gene prediction programs and/or cross species comparative genomic sequence analysis. The claimed microarray with these selected probes provides a valuable resource for high throughput gene discovery, the identification of alternatively spliced exons within a gene, the confirmation of predicted genes and exons, as well as providing expression verified single exon probes. It is Applicants’ believe that specific, substantial utilities are disclosed in the instant application specification, and these utilities are credible.

One of these utilities disclosed in the instant application for the claimed microarray is high throughput gene discovery. Applicants “have used the methods and apparatus of the present invention to identify more than 15,000 exons in human genomic sequence whose expression we have confirmed in at least one human tissue or cell type. Fully two-thirds of the exons belong to genes that were not at the time of our discovery represented in existing public expression (EST, cDNA) databases, making the methods and apparatus of the present invention extremely powerful tools for novel gene discovery” (page 24 line 33 through page 25, line 8, also page 61, lines 24 – 32). “(T)he observation that 1/3 of the arrayed genes exist in expression databases provides powerful confirmation of the power of our methodology — which combines bioinformatic prediction with expression confirmation using genome-derived single exon microarrays — to identify novel genes from raw genomic data” (page 83, line 29, through page 84, line 2). An artisan of ordinary skill in the genomics art would immediately appreciate that the two-thirds of the exons mentioned hereinabove belong to novel genes not known by the public at the time. The microarray of the instant invention is thus a useful tool for high throughput gene discovery from any eukaryotic genome averaging at least one intron per gene.

Another of these utilities disclosed in the instant application for the claimed microarray is the identification of alternatively spliced isoforms of genes among the large number of various cell types, developmental stages, and more importantly, physiologic

conditions. The microarray of the instant application proves to be "exceedingly useful in the high throughput identification of a large variety of alternative splice events in eukaryotic cells and tissues" (page 25 lines 9 – 17 and page 29 lines 7 – 18). The utility of these microarrays in the identification of alternatively spliced isoforms of genes is "further described in commonly owned and co-pending U.S. patent application serial no. 09/632,366, filed August 3, 2000, the disclosure of which is incorporated herein by reference in its entirety" (page 29, lines 11 - 14). Here, all of the predicted exons of a gene are included on the microarray and in the subsequent expression analysis (see the specification, especially Figures 11 – 13 and Example 4 of the co-pending US patent application serial no. 09/632,366).

Another of these utilities disclosed in the instant application for the claimed microarray is for verifying the expression of putative exons or genes predicted from genomic sequence (page 30 line 18 – 26 and page 47 line 27 through page 48 line 9). These expression verified sequences are also useful as gene-specific probes (page 28, lines 30 – 31).

Indeed, the utilities of the instant invention in gene discovery were initially proven in the section entitled "Verification of Gene Expression" of the instant application (see page 83). These utilities were further proven when Applicants succeeded in the characterization of an important cardiac myosin-like gene (US 6,686,188) and multiple

novel alternatively spliced isoforms (US 6,656,700) of a gene proven useful as a readily sampled marker for prenatal monitoring of fetal health and diagnosis of a number of human fetal abnormalities.

The instant application described multiple specific, substantial utilities for the claimed invention. Applicants respectfully submit that the claimed microarrays are useful. Withdrawal of the utility rejection, as well the 35 U.S.C. 112, first paragraph rejection is earnestly solicited.

Claim rejections – 35 USC §112

Claims 68, 69, 72 – 74, 80 and 81 are rejected under 35 USC § 112, second paragraph as, in the Examiner's view, being indefinite for failing to particularly point out and distinctly claim the subject matter with which applicants regard as the invention.

Regarding claims 68, 69, and 72 – 74, the Examiner states that the various sources from which the microarray may come as recited in these claims "are vague and indefinite as it is unclear as to how the source further limits the microarray or the sequence contained on the array." Claim 72 is further rejected because, in the Examiner's view, "the phrase 'at least in part' renders the claim indefinite".

Applicants respectfully traverse these rejections: one skilled in the art of molecular biology would well understand the metes and bounds of each of the rejected claims. The claims are definite and fully satisfy the requirements of the statute. Nonetheless, solely to expedite prosecution, applicants have amended independent claim 61, as well as dependent claims 68, 69 and 72, thus obviated the rejections. Applicants respectfully request that the rejections be withdrawn.

Claim 80 stands rejected because, the Examiner states, the phrase control probe is unclear. Applicants have amended the claim to read: "negative control probes for hybridization", thus obviates the rejection. Applicants respectfully request that the rejections be withdrawn.

Claim 81 stands rejected because, in the Examiner's view, there is insufficient antecedent basis for the limitation "in the eukaryotic genome" in line 4. Claim 81 is also rejected because, the Examiner states, "the phrase 'identically contiguous' is unclear".

Applicants have amended claim 81 to provide proper antecedent basis for the "eukaryotic genome". Regarding the phrase "identically contiguous", it is meant to say that in addition to the sequence from the predicted exon, the probe further contains sequence, base for base, the same as the sequence in the eukaryotic genome, surrounding the predicted exon (e.g. the flanking introns). In other words, the probe contains a

contiguous piece of genomic sequence, including the predicted exon, as well as some sequence from both of the flanking introns, base for base. The amendment and the clarification obviate the rejections. Applicants respectfully request that the rejections be withdrawn.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on May 28, 2004.

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